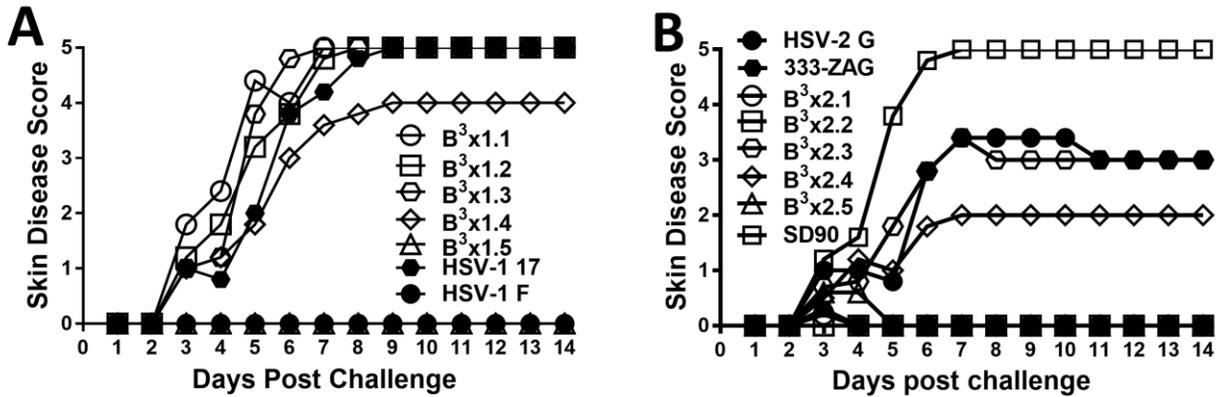
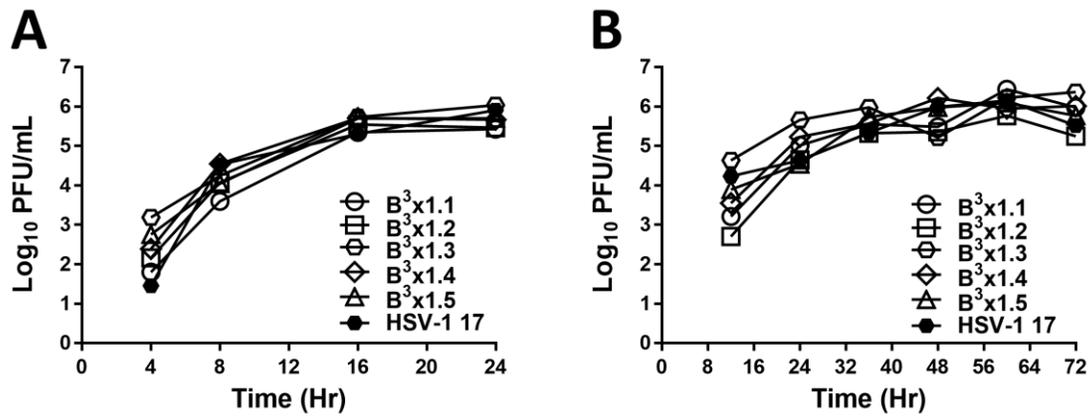


Supplemental Figure 1. HSV-2 Δ gD-2 protects against intravaginal or skin disease in a dose de-escalation study. C57BL/6 mice were primed and then 21 days later boosted subcutaneously (sc) with 5×10^4 PFU, 5×10^5 PFU, 5×10^6 PFU of HSV-2 Δ gD-2 or VD60 lysates (control). Mice were subsequently challenged 21 days after boost with an LD90 of HSV-2(4674) either (A) intravaginally or (B) via skin scarification and scored for disease (n=5 mice/group, line represents mean; see Methods for scoring scale).

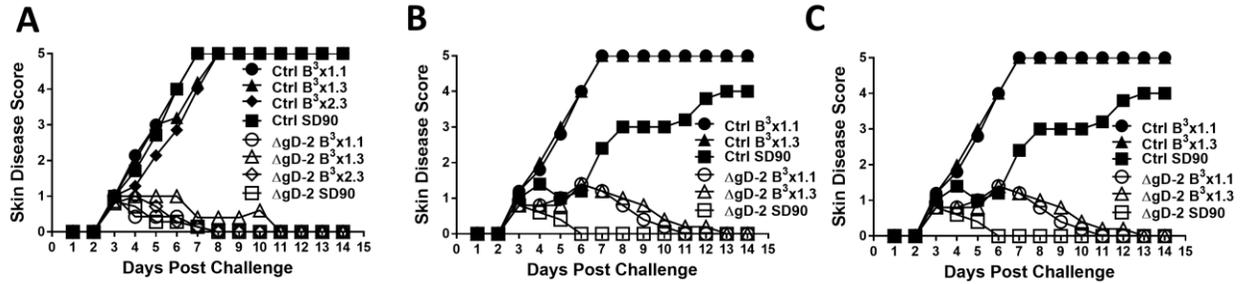


Supplemental Figure 2. HSV-1 and HSV-2 US and African clinical isolates and lab strains induce variable skin disease. Balb/C mice were infected by skin scarification with 1×10^5 PFU/mouse of each of the HSV-1 (A) or 5×10^4 PFU/mouse of each of the HSV-2 (B) isolates and scored for disease (n=5 mice/group, line represent mean disease score for the group at each day post-challenge).

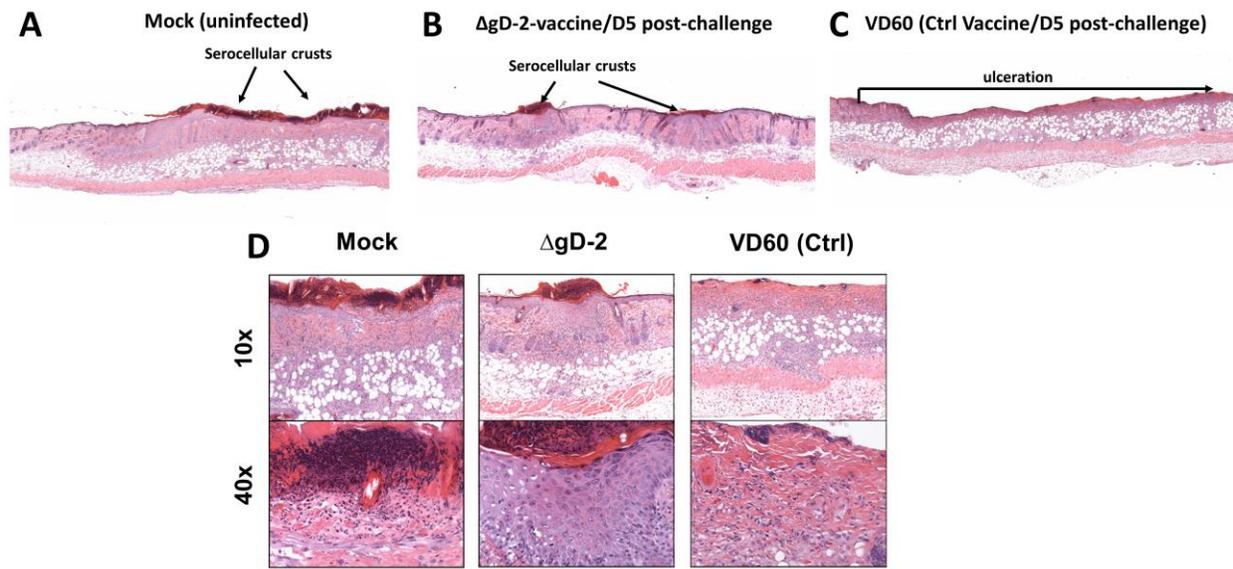


Supplemental Figure 3. Little difference in *in vitro* growth of HSV-1 clinical isolates.

Five HSV-1 clinical isolates (B³X1.1-B³x1.5) and the laboratory strain HSV-1(17) were evaluated for single-step (A) and multi-step (B) growth kinetics on Vero cells. Data is represented as mean log₁₀PFU per ml of combined supernatant and cell viral titer at each time point. Error bars were removed to clarify figure. There were no significant differences in growth.



Supplemental Figure 4. Mice vaccinated with HSV-2 ΔgD-2 exhibit minimal disease following challenge with clinical isolates of HSV-1 and HSV-2. C57BL/6 (n=7 mice/group) or Balb/C (n=5 mice/group) mice were immunized with ΔgD-2 or VD60 cell lysates (Control) and subsequently challenged with an LD90 dose of most virulent isolates and monitored disease on the skin. Disease scores for (A) C57BL/6 and (B) Balb/C mice. Additional C57BL/6 mice were challenged with 10 and 100 times (10x and 100x) the LD90 dose of SD90 and 10x the LD90 of Bx³1.1 and scored for disease (C). Line represents mean disease scores.



Supplemental Figure 5. HSV-2 Δ gD-2 vaccinated mice display decreased histopathology in their skin at day 5 post-challenge. Skin biopsies obtained from Δ gD-2 or VD60 lysate (control) immunized mice on day 5 post-challenge or unimmunized, uninfected (mock) mice were stained with H&E. Representative images at 4x magnification for mock (**A**), Δ gD-2 vaccinated (**B**) and control-vaccinated (**C**) mice are shown. (**D**) Areas of the same skin samples were imaged at 10x and 40x magnification to show inflammation and epidermal-dermal junction.